Historical Perspectives

The History and Development of Cardiac Transplantation

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The history of heart surgery, spanning only 100 years to date, has seen some of the most daring and persistent men and women in all of medical history. Many aspects of heart surgery, including such innovations as the heart-lung machine, aortic aneurysm surgery, and the correction of congenital heart defects, have provided future surgeons with an important lesson: diligent research can solve complex problems. The history and development of cardiac transplantation is particularly full of challenges that have been overcome, with the research phase alone spanning more than 90 years. During that time, essential contributions came from all over the world, including the United States, Russia, England, and South Africa.

As is typical of medical advancement, individual contributions did not stand alone but added to the experience of those who had come before. Even so, the work of a few particular groups deserves special recognition. Most notable is the Stanford team, led by Dr. Norman Shumway, who continued to transplant human hearts when other institutions had abandoned hopes for the operation. Largely because of the commitment of that team, cardiac transplantation has become a standard option in the treatment of end-stage heart disease. Currently, only the availability of donor hearts limits the number of cardiac transplantations performed worldwide. ***(Tex Heart Inst J 1999;26:198-205)***

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Tracing the history of surgical procedures back to their origins and reviewing the improvements made over time can provide insight into modern surgical practices. Such an exercise also serves as a reminder that diligent, original research can overcome difficult technical problems. Cardiac surgery is a particularly good example, because the entire history has occurred during the past 100 years, and all of the original publications are available to reveal the year-to-year progress. Particularly full of heroes and challenges that have been overcome, the history and development of cardiac transplantation represents one of the greatest triumphs of modern medicine.

From a chronological standpoint, the history of heart transplantation can be divided into the research era, the early clinical era, and the modern era; each era has produced landmark advances in surgical technique, organ preservation, and diagnosis and treatment of rejection. The clinical era began in 1964 with the 1st attempt at human heart replacement; the combined use of percutaneous transvenous endomyocardial biopsy and cyclosporin A initiated the modern era of heart transplantation in 1980.

The Research Era

Early Experimentation

During the late 1890s, Alexis Carrel began the 1st formal experiments with vascular anastomosis. Previous anastomosis of arteries and veins had invariably led to thrombosis and failure; Carrel would be the 1st to achieve success. Promising results led him to use this technique in novel ways, which included the movement of whole organs into heterotopic positions. In 1902, he attempted to transplant kidneys into the necks of dogs.[1] In his subsequent work with Charles Guthrie, "The Transplantation of Veins and Organs,"[2] he described many operations, including the 1st heterotopic heart transplant. The transplantation procedure began with the division of the carotid artery, the distal end of which provided blood flow to the pulmonary veins of the donor heart. The blood flowed through

the left atrium, the left ventricle, and the aorta into the distal end of the divided jugular vein. The proximal portions of the carotid artery and jugular vein provided blood flow to and from the right heart, respectively. It should be noted, however, that despite the successful perfusion of the coronary arteries, the heart was not providing circulatory assistance.

For his groundbreaking research, Carrel received the 1912 Nobel Prize in Medicine and Physiology and is known as the father of vascular and transplant surgery. Even after his success and recognition, Carrel's dream of heart transplantation would not be explored again for many years. It was not until 1933 that Mann and associates,[3] of the Mayo Clinic, published a complete report of 2 techniques for heterotopic cardiac transplantation. In their introduction, the authors wrote a passage alluding to allograft rejection, as it was understood from early experimental work on renal and glandular transplantation:

> . . . autotransplantation, that is, reimplantation of tissue or of an organ in the same subject is often successful, whereas homotransplantation, that is, implantation into another subject of the same species is rarely successful, regardless of the tissue or organ transplanted.[3]

In their heterotopic transplant experiments, Mann's group used either the proximal or the distal end of a divided carotid artery (techniques 1 and 2, respectively) to supply blood to the aorta of the donor heart and achieve coronary circulation. The coronary sinus blood returned to the right atrium (which was closed off at the venae cavae) and flowed into the right ventricle. It continued on through the pulmonary artery, which was anastomosed to the jugular vein. The authors reported that the heart began contracting "immediately after the coronary circulation was established" and the rate was "surprisingly constant from moment to moment."[3] Modern cardiac surgeons take for granted that the heart is extremely resilient, able to function outside of the thoracic cavity and even after a period of anoxia; but these points were being established for the very 1st time in those early studies. Mann's group described the allograft pulse as gradually fading from detection, and 8 days was the longest that they could keep the implanted heart alive.

Although both Carrel and Mann can be regarded as ahead of their time, no one was more advanced than Vladimir Demikhov, who was the next surgeon to experiment with heart transplantation. Demikhov was born in Russia in 1916. By 1940, he was working as an assistant in the department of human physiology at the M.V. Lomonosov Moscow State University. He had already developed an artificial heart that, despite being too big to fit entirely into the chest of a dog, could substitute for a dog's heart for as long as 5.5 hours.[4] Clearly a gifted and visionary surgeon, Demikhov began transplanting auxiliary hearts into the chests of dogs in 1946. He was the 1st to perform this "piggyback" heart operation, and within a few years these dogs were surviving as long as 32 postoperative days.

That same year, Demikhov also began the 1st series of combined heart-lung transplants, achieving 4- and 6-day survival in experimental animals between 1946 and 1955.[4] His most far-reaching and technically demanding achievement, however, was the 1st series of experiments in which the canine heart alone (as opposed to heart and lung) was successfully transplanted into the orthotopic position, at a time when hypothermia had not been used and heart-lung bypass had not been invented. His incredible procedure included end-to-side anastomoses of the donor aorta, pulmonary artery, and venae cavae to the corresponding recipient vessels, while the pulmonary veins of the donor heart were joined together and attached to the recipient left atrium. This allowed the recipient left atrium (closed off with a purse-string suture) to be left intact, and the nearly impossible challenge of pulmonary vein anastomosis was avoided. Beginning in 1951, Demikhov performed this operation 22 times, reporting 11.5- and 15.5-hour survival times by January of 1955.[5] This work presented the 1st evidence that a cardiac allograft could provide pumping function in a recipient animal.

Because Demikhov's research was not published in English until 1962, it remained unknown to those American researchers who might have pursued his results. In fact, heart transplantation disappeared from the literature after Mann's report[3] in 1933 but resurfaced in 1951 when Marcus, Wong, and Luisada,[6] from The Chicago Medical School, published their experience with heterotopic heart transplantation. In their introduction, they only hinted at the potential outcome of this research:

> Can such a graft actually function by receiving and delivering blood? Whether it might so function as to replace its counterpart in the host is a fantastic speculation for the future. On the other hand, such a grafted heart might serve as a test object for the physiologic and pharmacologic studies.[6]

Marcus and coworkers used a complicated technique that involved 3 dogs: a donor, a recipient, and a 3rd dog whose circulatory system was used to sup-

port the donor heart during the time that it was disconnected from the circulation. This "interim parabiotic perfusion," as they called it,[6] was used to place the heart into 2 configurations that were minor variants of those described by Mann. Theirs was the 1st method of preserving the donor heart during transplantation. It is interesting to note that this method is similar to C.W. Lillehei's brilliant clinical use of cross circulation,[7] in that an intact circulatory system was used for the perfusion of another. Moreover, after this publication by Marcus and coworkers in 1951, heart transplantation would never again disappear from the research literature.

Advances in cardiac transplantation during the next few years paralleled the rapid progress in heart surgery in general, as research began to benefit from the technologies of hypothermia and heart-lung bypass. The 1st use of hypothermia in heart transplantation was reported in 1953 by Neptune and colleagues,[8] from Hahnemann Medical College in Philadelphia. Although this was thought to be the 1st attempt at orthotopic transplantation of the heart-lung unit, it was later realized that Demikhov had accomplished this operation years before. After many failed attempts, Neptune's group successfully transplanted the heart-lung unit into 3 dogs, achieving survival times of 30 minutes, 4 hours, and 6 hours. These operations proved that the cardiac allograft was capable of assuming the circulatory load of the recipient. The authors explained that transplanting the heart and lungs together eliminated the "problem" of the pulmonary circulation; yet Demikhov had already successfully transplanted the heart alone, and without hypothermia.

In the meantime, Marcus and associates[9] were still at work. In 1953, they used interim parabiotic perfusion to achieve several different versions of heterotopic heart and heart-lung transplantation; the longest survival time for an allograft recipient was 48 hours.

Accelerated Research after Human Renal Transplantation

History was made on 23 December 1954 at the Peter Bent Brigham Hospital in Boston when Murray, Merrill, and Harrison[10] performed the 1st human renal transplantation in identical twins. Although the fact that the patients were twins simplified the procedure in terms of postoperative management, the 1st successful transplantation of a whole organ must have been both exciting and encouraging to anyone interested in organ transplantation. Between 1955 and 1964, researchers conducted various experiments that gradually improved animal survival times. Interestingly, longer survival made the problem of tissue rejection a reality, in contrast to previous experiments in which the animals had lived for only a brief time after the procedure.

In another triumph of technology, Webb and Howard,[11] from the University of Mississippi Medical Center, used a pump oxygenator for orthotopic heart-lung transplantation in 1957. They transplanted the heart with 1 lung and with both lungs, and they also used autotransplantation to study the effects of the operation itself on heart-lung function. The 2 researchers wrote that, although complete heart-lung transplantation was probably not feasible because of a failure of the denervated lungs to initiate spontaneous respiration, satisfactory cardiopulmonary function could be achieved when the heart and 1 lung were replaced. They concluded that this method, as well as transplantation of the heart alone, should be possible in human beings.

Webb, Howard, and Neely[12] in 1959 published a method for orthotopic transplantation of the heart alone, which had produced 12 successful transplants and survival as long as 7.5 hours. Ironically, their procedure involved the difficult anastomosis of all the pulmonary veins to the left atrium—a technique that would soon become unnecessary. The University of Mississippi researchers went on to make substantial advances in lung transplantation and, as will be discussed, they were also the 1st researchers to attempt heart transplantation in a human recipient.

In the 1st British contribution to heart transplantation, Cass and Brock[13] described several different attempts at autotransplantation in 1959. One of their techniques was notable because it left the recipient's left atrium, right atrium, and posterior septal crest partially intact. This was a variant of what Demikhov had done with the left atrium alone in order to avoid anastomosis of the pulmonary veins and the venae cavae. The inexperience of this group, however, produced discouraging results in terms of animal survival.

Further Advances in Research

The pace of research in pursuit of human heart transplantation quickened considerably when Dr. Norman Shumway and his group at Stanford University began publishing studies that would become a long and important list of achievements. In 1960, Lower and Shumway[14] described their experiments with orthotopic homotransplantation of the canine heart, using a rotating-disk oxygenator and the above-mentioned technique of partial atrial preservation. These attempts, unlike previous efforts, yielded impressive survival times. In a series of 8 transplants, 5 dogs survived for between 6 and 21 postoperative days. Although the preservation of the

recipient atrium had been described by others, including Cass and Brock, it was this report[14] that established the technique as a standard for the researchers and clinicians who followed. Even today, the "Shumway technique" is the preferred method of cardiac replacement.

Shumway and coworkers[15] continued their research, and in 1961 outlined their complete protocol for canine heart transplantation, which had resulted in survival times ranging from 6 hours to 8 days. In their introduction, they made a bold prediction:

> The homograft rejection mechanism can be avoided only when its nature is more clearly defined. . . . Further, the precise mechanism by which the host causes death of the homologous cells is not known. One must assume that, as these mechanisms are clarified, an appropriate means will be found of altering either the elaboration of the homologous antigen or the immunologic response of the host without injury to either graft or host.[15]

Knowing that these "means" were not imminent, the group concentrated on surgical technique and the preservation of the donor heart. They used isotonic saline at 4 °C to preserve the donor heart and ensure allograft function. In addition, they maintained the recipient dogs on cardiopulmonary bypass for a short time after completion of the operation, which allowed the heart to slowly assume the circulatory load.

Elsewhere, studies using autotransplantation were being performed in order to closely evaluate the effects of the operation itself on cardiac function. Researchers at the St. Louis University School of Medicine[16] published the results of 40 autotransplant operations and reached some discouraging conclusions. With only 13 of the animals living beyond the 2nd postoperative day, the researchers compared the hearts of these animals with the hearts of another group that had undergone a sham operation:

> This study emphasizes the hazards inherent in the technique of transplantation. . . . In all animals subjected to cardiac excision and reimplantation, edema developed which required thoracentesis and diuretics. Many died from congestive heart failure. In contrast, none of the animals subjected to the sham procedure showed this picture. This difference in the course of the two groups indicates a specific adverse effect of severing the heart from the body.[16]

What must have been confusing at this time was that in the same year, the Stanford group performed the same study with outstanding results.[17] The team explained that their 75% to 80% survival rate, in fact, reflected some early problems, including the need to bolster the aortic suture line and the occurrence of complete atrioventricular block. The difference in the results of these 2 studies[16,17] was never formally explained by either group, but it is likely that the extensive experience of the Stanford team had led to a technically superior procedure. With proof that the excised heart could be reattached and could function once again, researchers turned to a problem of much greater proportions—that of tissue rejection.

Rejection in renal transplant patients had been treated only with total body irradiation before 1960, when Goodwin introduced the 1st antirejection drug therapy: methotrexate and cyclophosphamide, with prednisone to control individual rejection episodes.[1] This innovation sparked the interest of heart surgeons, who immediately turned to experimentation. In 1962, Reemtsma and colleagues,[18] from Tulane University, reported the successful use of methotrexate for heterotopic heart transplantation in 21 canines. The results were significant, with the recipient animals surviving as long as 26 postoperative days. As the authors pointed out, the previous collective experience of heterotopic transplantation had yielded a maximum survival of only 10 days without immunosuppression. Although these new results were encouraging, they also revealed serious problems, such as the unusually high incidence of infection and drug toxicity associated with immunosuppressive therapy.

Quoting Reemtsma's success, Blumenstock and coworkers[19] published results of their use of methotrexate in dogs undergoing orthotopic heart transplantation. With deaths occurring as late as 18, 32, and 42 days postoperatively, this 1963 study produced the longest and most impressive results that had been achieved to date. Blumenstock's group showed, both functionally and histologically, that chemical immunosuppression could delay rejection in the orthotopic heart transplant recipient.

The Early Clinical Era

The encouraging experience of various research teams stimulated consideration of clinical trials with human beings. The University of Mississippi's team was the 1st to train for clinical application.[20] In the closing months of 1963, nurses and anesthesiologists were brought into the research laboratory for familiarization and full rehearsal for cardiac transplantation. The team had to consider many serious ethical issues, but one in particular needed to be

resolved before human heart transplantation could be performed. They explained that the likelihood was small that a potential donor would die at the exact time when a potential recipient needed a heart, "unless one were willing to halt mechanical support of respiration in a potential donor." By January of 1964, the decision had been made that the team would not halt the ventilation of a patient, and that if a donor heart was not provided by luck alone, they would consider using a chimpanzee as a donor.

Early that same month, the team was called to readiness when a potential recipient was declared.[20] The patient had a large thrombus that had embolized to the left heart. As the team tried to remove the thrombus, they decided to consider transplantation if the heart failed during the immediate postoperative period. This particular patient did not require transplantation, but the team found themselves in the same position on 23 January. With a potential recipient on the verge of death and the potential donor still alive, the heart of a chimpanzee was harvested. The heart was kept alive with mechanical coronary perfusion, and that part of the operation came to a successful end when the allograft began to beat steadily. The celebration was cut short, however, when the team realized that the chimpanzee heart could not handle the large venous return of a human being. Further circulatory support was abandoned, and the patient died 1 hour after being weaned from cardiopulmonary bypass. Although the outcome was not successful, more experience was gained, lessons learned, and conclusions drawn. In short, the latest failed attempt only fueled the interest in transplantation, which continued to build over the next several years.

On 3 December 1967, Dr. Christiaan Barnard[21] took the world by surprise when he transplanted a donor heart into a 54-year-old patient at the Groote Schuur Hospital in Cape Town, South Africa. The donor was a trauma victim with massive cerebral injuries. When she was pronounced dead, her heart was taken via the Shumway technique and kept on mechanical perfusion at 10 °C while the recipient was prepared. Barnard used a combination of local irradiation, azathioprine, prednisone, and actinomycin C for possible rejection. He did his best to keep the patient in a sterile environment, and the immediate postoperative course looked very promising. Nevertheless, the patient died of *Pseudomonas* pneumonia on the 18th postoperative day. Three days after Barnard performed the 1st transplantation of a human heart, a 2nd one was transplanted at the Maimonides Medical Center in Brooklyn, New York.[22]

Dr. Adrian Kantrowitz, who led the Brooklyn team, had already been a pioneer before December of 1967. His brother was a gifted engineer, and together they were responsible for the development and 1st successful clinical use of the modern-day intraaortic balloon pump. Kantrowitz and his team had gained considerable laboratory experience in cardiac transplantation and were as ready as any group at this time to progress to a human heart. Kantrowitz had thought that performing heart transplantation on puppies in the lab was beneficial, because a younger immune system might offer less resistance to an allograft.[22] Carrying this logic to human beings, infant transplantation would present the same advantages. Moreover, anencephalic babies could serve as donors.

On 6 December 1967, Kantrowitz and associates used an anencephalic donor heart to replace the heart of a 3-week-old patient diagnosed with type IA tricuspid atresia and atrial communication.[22] Although the age of this infant posed a daunting challenge, Kantrowitz performed the transplant under hypothermia with full circulatory arrest, achieving spontaneous sinus rhythm at 5:30 AM. Later that afternoon, the baby developed metabolic and respiratory acidosis and died, despite exhaustive attempts at resuscitation.

Exactly 1 month later, Shumway and his team undertook their 1st human heart transplant.[23] According to their report, the surgeons had to overcome a rather serious problem in the operating room. The donor heart was much smaller than that of the recipient; consequently, the surgeons had to tailor all of the anastomotic suture lines to attain sufficient circumference. The patient had received azathioprine and methylprednisolone preoperatively, and prednisone, azathioprine, and methylprednisolone after the operation. But rejection was not the source of this patient's problems. Oliguria had plagued the entire postoperative course, during which the patient required 2 laparotomies: 1 was an emergency cholecystostomy and the other was an exploration for severe upper-gastrointestinal bleeding. It was during the 2nd operation that gram-negative sepsis developed, and the patient died on the 15th postoperative day.

Another early clinical trial was conducted by Cooley and associates[24] at Baylor University College of Medicine. In their study, they achieved survival times that were significantly longer than those of previous studies. Beginning in May of 1968, Cooley and his team performed 10 human heart transplants, 1 heart-lung transplant, and even a sheep-to-human xenograft. They used blood-group compatibility, lymphocyte crossmatch studies, and a matching grade system in an attempt to predict the success of the transplant. In addition, they administered antilymphocyte globulin as an adjunct to the previously existing antirejection therapy. Cooley's group reported that 7 of the human heart recipients were alive as long as 4.5 months after transplantation.

These reports highlight the more successful procedures that were performed by the leading cardiothoracic surgeons of the day. However, their encouraging results were not representative of what was going on in the greater community of new heart transplant programs, which had developed seemingly overnight. During the year following Bernard's initial operation, 102 heart transplants were performed,[1] with one failure after another. Shumway summarized the situation:

> Suddenly heart transplants were being done in places where one would hesitate to have his atrial septal defect closed.[1]

It was not long before the inadequate understanding of the rejection process and the attendant inability to diagnose and treat rejection forced inexperienced groups to abandon heart transplantation efforts. Although this was a bleak moment in the history of cardiac transplantation, Shumway's group persisted. Dr. Kantrowitz, who was on the NIH review committee that visited Shumway's lab, provided some insight:

> The team at Stanford had a good understanding of the difficulties involved and embarked on a careful scientific clinical study. . . . The NIH Review Committee was wholeheartedly enthusiastic, finding that the research environment was particularly good, with a superb team approaching the immunologic issues, and that the academic institution was strongly encouraging.[25]

The commitment of the Stanford investigators and the NIH funding that they received proved to be worthwhile. In 1971, the group published their experience with 26 human heart transplant patients,[26] of whom 42% had survived for 6 months, 37% for 18 months, and 26% for 2 years. Early diagnosis of acute rejection was a major goal of postoperative care and the key to the survival of these patients. Previous laboratory experiences had shown that electrocardiographic changes, including decreased QRS voltage, arrhythmia, right shift of the electrical axis, and ST-T wave changes were findings of rejection, especially when coupled with the clinical findings of gallop heart sounds and hypotension. Therefore, electrocardiographic, clinical, and echocardiographic findings were used for the diagnosis of 60 episodes of rejection.

Although not perfect, these methods proved adequate to signal the need for methylprednisolone, actinomycin D, and antilymphocyte globulin; 57 of the 60 recognized episodes of rejection were effectively treated.[26] It was found that the incidence and severity of rejection peaked within the first 2 months after surgery and then decreased significantly. In 1973, with the protocol of allograft monitoring and drug administration virtually unchanged, Shumway's group reported the results of their 3-year experience with 29 patients.[27] The overall actuarial survival rate was 49% at 6 months, 37% at 18 months, and 30% at 2 years.

As more experience with long-term survivors was gathered, Shumway described and characterized several new problems.[27] Thirteen of his patients receiving allografts had been discharged, in good health, to their homes. After that time, a total of 12 rejection episodes in 5 of the patients were diagnosed by the usual methods. These later rejection episodes, however, were milder than those seen immediately after transplantation, and the term "late acute rejection" was adopted to distinguish such occurrences from the earlier, more severe type of acute rejection. Treatment with prednisone was successful in all 5 of these patients; so the long-term survivors were not lost to late acute rejection. Instead, the limiting factor for these patients was found to be "chronic rejection," which manifested as diffuse allograft vasculopathy. This condition led to episodes of sick sinus syndrome (sinus ischemia) and myocardial infarction, which claimed the lives of the long-term survivors.

In another 1973 accomplishment, the Stanford group formulated a new technology[28] that would raise human heart transplantation to the next level. Percutaneous transvenous endomyocardial biopsy was a technique 1st used in Shumway's laboratory animals: a catheter bioptome was introduced through the right internal jugular vein into the right ventricle, which allowed a small tissue sample to be obtained with minimal risk to the patient. Before this technology, it had always been necessary for surgeons to weigh the apparent severity of the clinical findings and electrocardiographic changes of rejection against the possibility of unnecessarily increasing the patient's immunosuppressive medication if the diagnosis of rejection proved incorrect. A definite correlation could now be made between the histologic events occurring in the myocardium and the signs and symptoms of rejection.

Percutaneous transvenous endomyocardial biopsy was immediately added to the protocol at Stanford, including serial biopsy evaluations in the immediate postoperative period to confirm the slightest signs of allograft rejection. By 1974, the Stanford experience totaled 59 human heart transplants, with actuarial survival rates of 43% at 1 year, 40% at 2 years, and 26% at 3 years.[29] More transplant experience and longer patient survival times meant a better understanding of the timing of the rejection process, and survival rates of the transplant patients at Stanford

climbed slowly during the next few years. Indeed, it is likely that Shumway had, by the late 1970s, achieved the very best results possible with the technology that was currently available. One more step was necessary to make successful cardiac transplantation a reality: the development of a superior immunosuppressive regimen.

The Modern Era

Cyclosporin A was not developed and used in transplant patients overnight, as is commonly believed. It was gradually introduced into in vitro research, then into animal research, and finally into human patients during a 4-year period. J.F. Borel 1st reported the immunosuppressive effects of cyclosporin A in 1976.[30] A fungal metabolite isolated from Swiss soil samples, cyclosporin A was the 1st agent that acted selectively on lymphocytes. The 3 June 1978 issue of *The Lancet* contained 2 articles that described the 1st uses of cyclosporin A in experimental animals.[31,32] The 2nd of those papers[32] was especially important, because the researchers had used porcine cardiac allografts to test the in vivo immunosuppressive potential of the drug. The investigators concluded:

> Cyclosporin A is more effective in suppressing rejection than any other drug that we have used in pigs with orthotopic cardiac allografts. . . . Cyclosporin A is sufficiently non-toxic and powerful as an immunosuppressant to make it an attractive candidate for clinical investigation in patients receiving organ grafts.[32]

Shumway immediately began experimenting with cyclosporin A and incorporated its use into his clinical practice in 1980. After trying 3 different dosage protocols, his team found one that was effective. In December of that year, the 1-, 2-, and 3-year survival rates for the overall transplant experience at Stanford were 63%, 56%, and 52%, respectively. Five years later, the survival rates were 83%, 75%, and 70%, respectively. Thus, the introduction of cyclosporin A brought cardiac transplantation to its current level of acceptance and success.[33] Worldwide interest in heart transplantation for the treatment of end-stage heart disease was revived, and the frequency of heart transplantation increased exponentially.

On 1 November 1984, Cooley and associates,[34] from the Texas Heart Institute and Texas Children's Hospital, performed orthotopic heart transplantation in an 8-month-old infant, which was the 1st successful attempt in such a young patient. She had end-stage cardiac disease secondary to endocardial fibroelastosis and received a heart from a 2-year-old girl who had been declared brain-dead. Despite the administration of cyclosporin A and steroids, the patient experienced a severe episode of allograft rejection on the 7th postoperative day and another, moderate episode on the 22nd day. Nonetheless, she was well enough to go home on the 28th postoperative day.[34] The girl led a remarkably healthy life until November of 1997, when she died of transplant coronary artery disease.* This was just 1 notable example out of 9,200 heart transplant operations performed between 1980 and 1988.[35]

In 1990, the annual number of heart transplants began to level off—not because the operation had proved unsuccessful, but because of a limited availability of donor hearts.[36] It seems unfortunate that science and technology could make such an operation possible, only to have its utility limited by people's lack of awareness or their unwillingness to agree to organ donation. Be that as it may, it is the patients who have died while waiting for donor hearts who have inspired the latest mechanical and biological attempts at cardiac assistance, such as left ventricular assist devices, skeletal muscle ventricles, cardiomyoplasty, and many others. Perhaps one day, the development of an efficient, total artificial heart that is permanently implantable will negate the need for cardiac transplantation. Working toward this goal, we must not forget the foremost lesson bestowed by the history of cardiac surgery: Nothing can take the place of a well supported and well planned research effort for solving the most difficult of medical problems.

*Personal communication. Branislav Radovančević, 9 July 1999.

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